REMARKS

Claim 1 is pending in this application. Claim 1 has been rejected. Reconsideration is respectfully requested in light of the following remarks.

I. Rejection of Claims Under 35 U.S.C. §103

Claim 1 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Ueno et al. (1988) in view of U.S. Patent 4,624,965 ('965). The Examiner suggests that it would have been prima facie obvious for one of ordinary skill in the art to employ a dose of chlorpheniramine in a method of treating motion sickness as taught by Ueno et al. (1988) and that since both chlorpheniramine and bromopheniramine are old, well-known anti-histamines and are therapeutic equivalents, their dosage is the same. Thus, the basis for adjusting the dosage in the '965 patent so that the dosage of chlorpheniramine is the same as that of bromopheniramine is to be reasonably expected to be useful for treating motion sickness. Applicants respectfully disagree with the Examiner's conclusions.

First, Applicants respectfully point out that the Examiner's statements that the dosages of these drugs are the same based on citing the Drug Information Handbook is totally incorrect. Review of the sections on the Handbook provided entitled "Usual Dosage" reveals that the statements for the two drugs are NOT the same. There is some overlap in dose ranges but the statements are NOT identical. For example, oral doses in children are stated to start at 0.35 mg/kg/day for chlorpheniramine but at 0.125 mg/kg/day for brompheniramine. For adults given chlorpheniramine i.m., i.v., or s.c., the maximum dosage stated

is 20 mg while it is 10 mg for brompheniramine. These statements indicate that bromopheniramine is actually more potent as an anti-histamine, not equally potent as suggested by the Examiner.

Further, since the Examiner has not specifically addressed Applicants arguments filed in the reply dated May 7, 2007, Applicants feel it is important to reiterate some of those arguments that are based on sound and general principles of pharmacology. Applicants again remind the Examiner that the only data provided in U.S. Patent No. 4,624,965 discloses administration of therapeutic agents intra-nasally as anti-emetic and anti-nausea agents. Brompheniramine is mentioned as one of a group of selected agents. The patent teaches administration of from 5 to 75 mg of the agents nasally. However, no data are provided showing the anti-nausea effects of bromopheniramine. The only data provided showing actual anti-nausea effects of drugs are for metoclopramide or diphenhydramine. Nowhere does the '965 patent teach or suggest administration of any agent by a route other than intranasally, nor actual efficacy or pharmacological effect data on the use of the specific agent suggested by the Examiner, brompheniramine, at any dose. Therefore, the Examiner's positions regarding these references lack any basis in standards of basic pharmacology, the standards that would be applied by one of skill in the art.

Moreover, it is a general principle of pharmacology that efficacy of a drug is effected by the route of administration. In the case of the instant invention, the Examiner has suggested that data from intranasal administration of a different drug predict what one of skill would expect to see with an entirely different drug administered by an entirely different route. In

the specification as filed, the data provided to enable the claimed invention is based on administration of chlorpheniramine orally to humans. In the '965 patent cited by the Examiner, the drugs metoclopramide or diphenhydramine were shown to have anti-nausea effects when administered intranasally at doses of between 5 and 75 mg, not orally. No data on efficacy, by any route of administration, are provided for brompheniramine as suggested by the Examiner. The Drug Information Handbook also fails to provide any dosage information for oral administration of either drug as an anti-motion sickness drug. The drugs are listed in the Handbook as anti-histamines for use to treat symptoms of allergic rhinitis only.

It was also pointed out in the previous reply that it is a general principle of pharmacokinetics (the scientific discipline that studies how a drug arrives at its site of action to produce its effects, and how a route of administration affects the required effective dose of a drug) that a drug administered intranasally would have a different dose-response relationship for efficacy than that same drug would have if administered orally (see chapter 1 of *Goodman & Gilman's: The Pharmacological Basis of Therapeutics*, 10th edition. 2001. J.G. Hardman and L.E. Limbird (eds.), McGraw Hill: New York). For example, it is well-established that lower doses of a drug are administered intranasally in order to produce the same magnitude of efficacy/effects that are seen following oral administration (Salib, R.J. and P.H. Howarth. 2003. *Drug Safety* 26:863-893; see abstract). Therefore, contrary to the Examiner's suggestion, one of skill would not use data on intranasal administration of any drug to predict a dose level that would be effective orally for

the same drug, let alone an entirely different drug (brompheniramine).

The arguments made in the previous reply were further supported by an example of an FDA-approved intranasal anti-histamine agent, azelastine. As discussed, azelastine is a drug that is available as an intranasal formulation for treatment of allergic rhinitis that is from a different chemical class than chlorpheniramine, but like chlorpheniramine, has histamine receptor blocking activity (Salib, R.J. and P.H. Howarth. 2003. *Drug Safety* 26:863-893; see page 870). The recommended effective intranasal dose of azelastine is about 255 micrograms twice a day (2 sprays of 137 micrograms twice a day; Salib, R.J. and P.H. Howarth. 2003. *Drug Safety* 26:863-893; see page 870). In contrast, the effective oral dose of azelastine is described in the published medical literature to be in the range of 4 to 8 milligrams twice of day (Riethmuller-Winzen, H. et al. 1994. *Arzneimittalforschung* 44:1136-1140; see abstract). Therefore, the effective intranasal dose is 20 times lower than the dose shown to be effective orally. The Examiner is thus incorrect in suggesting that the '965 patent provides useful data for one of skill to set a dose of chlorpheniramine for use orally. The '965 patent provides data on entirely different drugs (metoclopramide and diphenhydramine) given intranasally. This patent can only inform one of skill about what is known concerning intranasal dosing, namely that drugs can be administered intranasally at lower doses than are given orally and would be expected to have efficacy at these lower doses if given intranasally.

In order to establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must

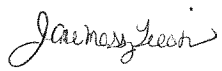
be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the cited prior art fails to teach the invention as claimed which is use of chlorpheniramine at a specific dose to decrease the signs and symptoms of motion sickness. The art, when combined, teaches use of chlorpheniramine only at much higher doses, 2 orders of magnitude higher doses, or teaches use of entirely different drugs intranasally. One of skill would not expect that data on an entirely different drug given by the intranasal route would suggest that chlorpheniramine given orally at 12 mg would be an effective drug to decrease the signs and symptoms of motion sickness. The Examiner's conclusions are without basis in the general principles and standards of pharmacology. Accordingly, the prior art references cited fail to establish a case of *prima facie* obviousness. Withdrawal of this rejection is respectfully requested.

II. Conclusion

The Applicants believe that the foregoing comprises a full and complete response to the Advisory Action of record.

Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,



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